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(54) Oral pharmaceutical composition.

(57) A sustained release, oral pharmaceutical composition in solid unit dosage form, for application to the mucosa of the oral or nasal cavity, comprises compressed, mucosa adhesive cellulose, coated granules, the granules comprising a drug, a higher aliphatic alcohol and a hydrated water soluble hydroxyalkyl cellulose.

Preferably the composition is in the form of a buccal tablet, especially a kidney shaped buccal tablet. Preferred materials are morphine as the drug, hydroxypropyl cellulose as the mucosa adhesive cellulose, cetostearyl alcohol as the aliphatic alcohol and hydroxyethyl cellulose as the water soluble cellulose.

The composition has enhanced adherent properties (to the mucosa) and prolongs the bioavailability of the drug.

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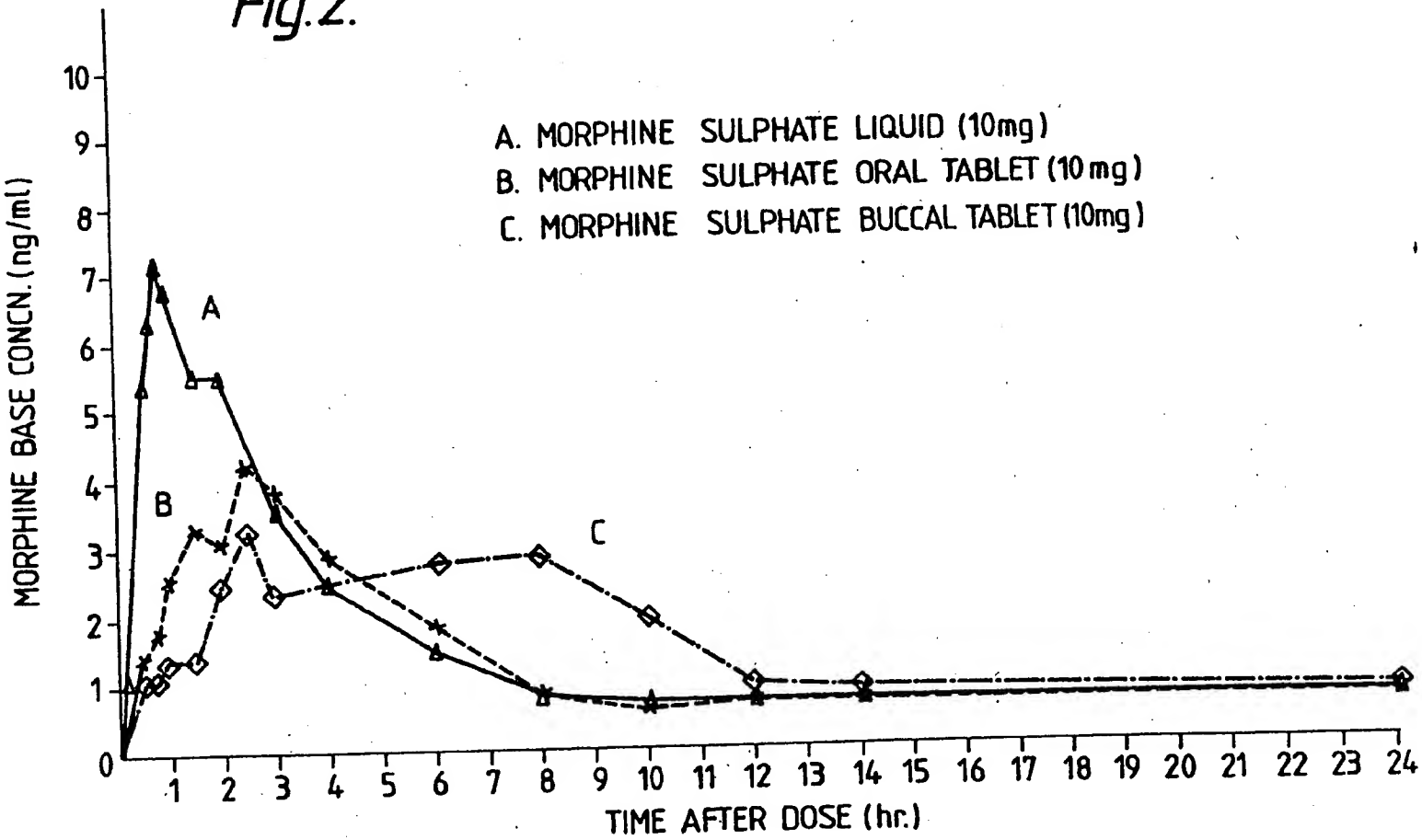
Fig.2.


A. MORPHINE SULPHATE LIQUID (10mg)
B. MORPHINE SULPHATE ORAL TABLET (10 mg)
C. MORPHINE SULPHATE BUCCAL TABLET (10mg)
MORPHINE BASE CONCN. (ng/ml)
TIME AFTER DOSE (hr.)
A
B
C
0
1
2
3
4
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ORAL PHARMACEUTICAL COMPOSITION

The present invention relates to a sustained release, oral pharmaceutical composition and, in particular, to an oral vehicle adapted for application to the mucosa of the oral or nasal cavity, especially within the buccal cavity.

The administration of drugs using oral vehicles retained in the buccal cavity is known. Such administration is generally effected by inserting an oral vehicle (e.g. a tablet) containing a drug into the buccal cavity of the patient's mouth and then pressing the vehicle against the mucosa of the cheek or the gum until it adheres.

Absorption of the drug in the vehicle generally occurs directly through the mucosa at the inner surface of the cheek and/or gum into the patient's bloodstream. In some cases, however, the drug may be absorbed gastrically or enterally by the absorption of drug contained in swallowed saliva.

The buccal method of drug administration has considerable advantages over adminstration by, for example, swallowing a tablet or injection. One advantage is that administration can be discontinued at any time (e.g. when undesired effects arising from the administration are identified) simply by removing the remainder of the vehicle. Another advantage, over oral administration, is that first pass, drug metbolism may be avoided.

A particular problem associated with the buccal administration of drugs, however, is that the oral vehicle containing the drug tends, after a period, to become detached from the mucosa. At best this can be merely inconvenient, at worst it may lead to the patient swallowing the vehicle.

It is an object of the present invention to provide a sustained release, oral pharmaceutical composition having improved properties of adherence to the mucosa within the oral or nasal, especially buccal cavity.

It is a further object of the present invention to provide an oral vehicle prepared from the improved composition and shaped to facilitate attachment within the buccal cavity.

Further objects and advantages of the present invention will become apparent from the following detailed description thereof.

According to the present invention, therefore, there is provided a sustained release, oral pharmaceutical composition in solid unit dosage form, for application to the mucosa of the oral or nasal cavity, comprising compressed, mucosa-adhesive cellulose coated granules, the granules comprising a drug, a higher aliphatic alcohol and a hydrated water soluble hydroxyalkyl cellulose.

Preferably the solid unit dosage form is an oral vehicle for attachment within the buccal cavity.

It is an important feature of the present invention that the granules used to prepare the solid unit dosage form (e.g. tablet) comprise extragranular mucosa-adhesive cellulose which improves the attachment of the dosage form to the oral or nasal mucosa, especially within the buccal cavity.

Preferably the extragranular, mucosa adhesive cellulose is applied to the granules in the form of a powdered solid rather than a solution. This allows greater control over the water content of the granules, avoids swelling of the granules and also avoids an unnecessary drying step.

The present inventors have surprisingly found that by employing extragranular cellulose adhesive, especially powdered adhesive, the adherent properties of the resulting dosage form are significantly greater than those of a dosage form having intragranular adhesive only.

The mucosa adhesive cellulose may be, for example, a carboxyalkyl cellulose, such as sodium carboxymethyl cellulose or a hydroxyalkyl cellulose, such as hydroxypropylmethyl cellulose. Preferably, however, hydroxypropyl cellulose (HPC), especially that sold by the Hercules Powder Company as Klucel HF (Trade Mark), is the mucosa adhesive material.

Preferably, the mucosa adhesive cellulose is a high molecular weight material having a number average molecular weight above 200,000, especially above 500,000.

Surprisingly, when HPC is employed as the adhesive in the present formulation it is found to give the dosage form adhesive properties superior to those achieved using previously preferred adhesives, such as Karaya gum and acrylic acid polymers (e.g. carbopol gel) or mixtures of these adhesives with other known binders.

The concentration of extragranular adhesive cellulose (as a proportion of the total dosage form weight) is preferably between 2% and 15% (w/w), especially between 4% and 10% (w/w). Prior to compression, the granules coated with mucosa-adhesive cellulose will, preferably, have a granule size of less than 1000μm.

The higher aliphatic alcohol is an aliphatic alcohol containing from 8 to 18 carbon atoms which is optionally substituted by a further aliphatic group containing from 8 to 18 carbon atoms. Suitable alcohols include lauryl alcohol, myristyl alcohol, stearyl alcohol, or, which is preferred, cetyl alcohol and cetostearyl alcohol. The higher aliphatic alcohol, together with the water soluble hydroxyalkyl cellulose, serves to control the release of the drug from the composition. The level of alcohol in the composition will therefore be determined by the

rate of drug release required. Generally, however, the composition will contain between 5% and 35% (w/w), especially 10% and 30% (w/w), (as a proportion of the total dosage form weight) of the higher aliphatic alcohol.

The hydroxyalkyl cellulose is a hydroxy lower alkyl ether of cellulose and is preferably selected from the group consisting of hydroxymethyl, hydroxyethyl, hydroxypropyl and hydroxypropylmethyl cellulose, with hydroxyethyl cellulose (for example Natrosol 250 HX, Trade Mark, Hercules Powder Company) being particularly preferred. The hydroxyalkyl cellulose, together with the higher aliphatic alcohol, serves to control the release of the drug from the composition. The level of hydroxyalkyl cellulose in the composition will therefore be determined by the rate of drug release required. Preferably the composition will contain between 2% and 15% (w/w), as a proportion of the total dosage form weight, of the hydroxyalkyl cellulose.

It should be noted that when the water-soluble hydroxyalkyl cellulose used in the present composition is also the composition's mucosa adhesive, then the amount of hydroxyalkyl cellulose present in each dosage form is at least the sum of the hydroxyalkyl cellulose added as water-soluble hydroxyalkyl cellulose and the hydroxyalkyl cellulose added as extragranular adhesive.

The drug employed in the present composition is preferably absorbable through the oral or nasal mucosa. In some instances, however, drugs that are absorbed gastrically and/or enterically (rather than via the mucosal route) may be employed. In a still further instance, the drug may be one that acts locally in the mouth, for example in the treatment of mouth ulcers. Suitable medicaments will be well known to those skilled in the pharmaceutical art. Listed below are certain of the drug categories within which are classed a number of the drugs that may be employed in the present composition.

(a) Analgesic agents; e.g. morphine, or analogues thereof, phenazocine, pentazocine, buprenorphine;

(b) Anti-inflammatory agents; e.g. ibuprofen, indomethacin, acetaminophen, phenacetin, aspirin, aminopyrine, sulpyrine, phenylbutazone, mefenamic acid, flufenamic acid, ibufenac, colchicine, probenecid, ethenzamide, salicylamide, ketoprofen, flurbiprofen, diclofenac, clidanac, alclofenac, sulindac, piroxicam;

(c) Antihistamines, e.g. clemastine fumarate, mepyramine, diphenylhydramine hydrochloride, dexchlorpheniramine maleate;

(d) Topical anaesthetics, e.g. benzocaine, procaine, lidocaine;

(e) Vasodilators, e.g. nitroglycerin, nifedipine, papaverine, isosorbide dinitrate, diltiazem, nicardipine;

(f) Antitussives and expectorants, such as codeine phosphate and isoproterenol hydrochloride;

(g) Hormones; e.g. insulin, vasopressin and heparin;

(h) Diuretics, e.g. ethacrynic acid and bendrofluazide;

(i) Anti/hypotensives, e.g. propranolol and clonidine;

(j) Anti-neoplastic agents, e.g. cytarabine and doxorubicin;

(k) Antidiabetic drugs, e.g. chlorpropamide and glibenclamide;

(l) Bronchodilators, such as albuterol - (salbutamol), ipratropiumbromide;

(m) Antiarrythmic agents, e.g. verapamil;

(n) Anti-inflammatory steroids, e.g. hydrocortisone, prednisone, prednisolone, triamcinolone, dexamethasone, betamethasone;

(o) Antibiotics or Fungicides, e.g. tetracyclines, leucomycins, fradiomycins, penicillins, cephalosporins, erythromycins;

(p) Chemotherapeutic agents, e.g. sulphathiazole, nitrofurazone, clotrimazole;

(q) Cardiac tonics, e.g. digitalis, digoxin;

(r) Oral antiseptics, e.g. chlorhexidine, hexylresorcinol, dequalinium chloride and ethacridine;

(s) Antiasthmatics, e.g. disodium cromoglycate;

(t) Drugs acting on the central nervous system, e.g. diazepam and estazolam;

(u) Anti-epileptics, e.g. phenytoin, meprobamate and nitrazepam;

(v) Anticholinergics, e.g. scopolamine;

(w) Muscle Relaxants e.g. baclofen, dentrolene sodium, cyclobenzaprine hydrochloride;

(x) Beta-blocker, e.g. pindolol;

(y) Antiarteriosclerotic agents, e.g. clofibrate, pentoxifylline;

(z) Drugs for treatment of ulcers, e.g. cimetidine, ranitidine;

Other, e.g. nicotine.

It will be appreciated that the drug may be added to the present composition not only in its free form, but also as a simple pharmacologically acceptable derivative, such as an ether, an ester, an amide, an acetal, a salt and the like. In some cases, such derivatives may actually be preferred.

Particularly preferred drugs for use in the present composition are morphine, nifedipine, phenazocine, verapamil and salbutamol.

These drugs can be used either singly or as a mixture of two or more. The amount of drug to be blended in a solid dosage unit will generally be enough to maintain a therapeutic level of the drug in the bloodstream for a predetermined period.

In addition to the constituents discussed above, the present pharmaceutical composition may also contain certain of the known excipients, such as lubricants, binders, vehicles, colouring agents, taste controlling agents and odour controlling agents, that are employed to improve the appearance, odour or taste of pharmaceutical preparations.

In a particularly preferred embodiment of the present composition, the granules contain between 2% and 15% (w/w), especially between 4% and 10% (w/w), of a binder to improve the binding and strength of the dosage form. Suitable binders include starch, dextrin, tragacanth, gelatin, polyvinylpyrrolidone, polyvinylalcohol or, which is especially preferred, a mucosa adhesive cellulose such as a carboxyalkyl cellulose or a hydroxyalkyl cellulose especially sodium carboxymethyl cellulose, hydroxypropylmethyl cellulose or, most especially, hydroxypropyl cellulose. Compositions according to this invention having both extragranular adhesive cellulose and intragranular adhesive cellulose (as binder) have been found to exhibit particularly good qualities of adhesion and strength.

It should be noted that when the same cellulosic material is used in the present composition as the water soluble hydroxyalkyl cellulose, the extragranular mucosa adhesive cellulose and the binder, then the amount of cellulosic material present in each dosage form is at least the sum of that added as water-soluble hydroxyalkyl cellulose and that added as binder and extragranular adhesive.

The present composition is prepared by compressing mucosa-adhesive cellulose coated granules of a mixture of a drug, a higher aliphatic alcohol and a hydrated water soluble hydroxyalkyl cellulose.

The mucosa-adhesive cellulose coated granules may be prepared in a number of ways. For example, the drug may first be incorporated in the higher alcohol or the cellulosic material prior to blending this with the remainder of the granules' constituents. Alternatively, and preferably, the drug may first be mixed with both the water soluble hydroxyalkyl cellulose and a binder before this mixture is blended with the higher alcohol.

The hydration of the water soluble hydroxyalkyl cellulose is effected at any convenient stage during the mixing of the granules' ingredients. It must be carried out carefully since excessive hydration of the hydroxyalkyl cellulose results in an unmanageable granular mass, whilst insufficient hydration results in an erratic and inferior release rate of medicament from the final composition. The degree of hydration is in practice preferably that obtained by the addition of a quantity of water between 1 and 5, especially, 2 and 3 times, the dry weight of the water soluble hydroxyalkyl cellulose.

Once the granules' ingredients have been mixed and hydrated they are then granulated and sieved to afford granules of a suitable granule size, preferably less than 1000μm. Finally the granules are mixed with extragranular mucosa adhesive cellulose to form mucosa adhesive cellulose coated granules.

It is important to note that the above methods and processes of granule formation are merely illustrative. Other preparations of the present mucosa adhesive coated granules will be immediately apparent to those skilled in this art.

The compressed granules may be formed into any suitable oral dosage form by the use of, for example, a punch, die or press. In order to facilitate the use of the present composition in the mucosal, especially buccal, administration of drugs, however, there is provided, in a further aspect of the present invention, a kidney-shaped oral vehicle adapted to fit closely the shape of the buccal cavity. Such an oral vehicle may be prepared using kidney shaped punches and dies.

Oral dosage units according to the present invention in the form of kidney-shaped oral vehicles have been found to be particularly convenient in the mucosal, especially buccal, administration of the drugs. It has been found that most patients may eat and drink freely whilst the kidney shaped oral vehicle is in position.

Sustained release, oral pharmaceutical compositions and oral vehicles according to this invention, as well as processes for preparing both compositions and vehicles, will now be described by way of example only.

A kidney-shaped oral vehicle according to this invention is particularly exemplified by reference to Figure 1 in which a plan, a side elevation and a rear elevation is shown.

Figure 2 shows the morphine plasma level achieved (as a function of time) by four patients using three morphine sulphate formulations.

Figure 3 shows the morphine plasma levels achieved (as a function of time) by nine patients using a buccal morphine tablet prior to surgery.

Example 1

The following ingredients were used to prepare one thousand tablets (200 mg total weight, 10 mg of morphine sulphate).

Ingredient	%	Weight (gm)
Morphine Sulphate	7.5	10.0
Mannitol	25.0	50.0
Lactose (Anhydrous)	15.0	35.0
Hydroxyethyl cellulose (Natrosol 250 HX)	13.3	26.6
Hydroxypropyl cellulose (Klucel HF)	12.5	25.0
Cetostearyl Alcohol	26.7	53.4
Water	q.s.	q.s. (approx. 65 g.)

The morphine sulphate, mannitol, lactose, hydroxyethyl cellulose and hydroxypropyl cellulose (15g., added as a binder) were dry blended until thoroughly mixed. The mixture was then hydrated - (approx. 65g.) until a wet granular mass was obtained. The hydrated material was then partially dried in a Fluid Bed Dryer (FBD) at 60¤C, granulated and sieved through a 12 mesh screen. The granulated material was then completely dried in the FBD at 60¤C, regranulated and sieved through a 16 mesh screen.

To the warmed morphine sulphate containing granules was added molten cetostearyl alcohol and the whole was mixed thoroughly. This mixture was allowed to cool in the air, regranulated and sieved through a 16 mesh screen.

The extragranular hydroxypropyl cellulose - (10g.) was then added and mixed with the granules, until at least a substantial proportion of the granules had a coating of hydroxypropyl cellulose.

Finally the coated granules were compressed and formed, using a kidney-shaped punch, into kidney-shaped tablets. This process afforded one thousand 200 mg. tablets, each containing 10 mg. of morphine sulphate.

If desired the tablets could then be coated using standard procedures.

Example 2

The method of Example 1 was followed except that the amount of morphine sulphate employed was increased to 20 g. and the amount of lactose employed was reduced to 25 g.

Example 3

The method of Example 1 was followed except that the amount of morphine sulphate employed was increased to 30 g. and the amount of lactose employed was decreased to 15 g.

Example 4

The method of Example 1 was followed except that sodium carboxymethyl cellulose replaced hydroxypropyl cellulose as the mucosa adhesive cellulose and binder.

Example 5

The method of Example 1 was followed except that morphine sulphate was replaced by nitroglycerin (5g.), added as a 1 in 10 blend of nitroglycerine and lactose, the amount of anhydrous lactose being reduced to zero.

Example 6

The following ingredients were used to prepare one thousand tablets (200 mg. total weight, 20 mg. nifedipine).

Ingredient	%	Weight (gm)
Nifedipine (micronised)	10	20
Xylitol	25	50
Anhydrous Lactose	42.75	85.5
Hydroxyethyl cellulose (Natrosol 250HX)	3.25	6.5
Hydroxypropyl cellulose (Klucel HF)	10	20
Sodium carboxymethyl cellulose (Blanose 7MFD)	2.5	5
Cetostearyl alcohol	6.5	13
Water		25

The nifedipine, xylitol, lactose, hydroxyethyl cellulose and hydroxypropyl cellulose (15g, added as a binder) were dry blended until thoroughly mixed. The mixture was then hydrated (approx. 25ml.) until a wet granular mass was obtained. The hydrated material was then partially dried in a Fluid Bed Dryer (FBD) at 60¤C, granulated and sieved through a 12 mesh screen. The granulated material was then completely dried in the FBD at 60¤C, regranulated and sieved through a 16 mesh screen.

To the warmed nifedipine containing granules was added molten cetostearyl alcohol and the whole was mixed thoroughly. This mixture was allowed to cool in the air, regranulated and sieved through a 16 mesh screen.

The extragranular hydroxypropyl cellulose (5g) and sodium carboxymethyl cellulose (5g) was then added and mixed with the granules, until at least a substantial proportion of the granules had a coating of hydroxypropyl cellulose. Finally the coated granules were compressed and formed, using a kidney-shaped punch, into kidney-shaped tablets.

This process afforded one thousand 200mg. tablets, each containing 20mg. of nifedipine.

Example 7

The method of Example 6 was repeated with the following ingredients,

Ingredient	%	Weight (g.)
Buprenorphine	0.25	0.5
Anhydrous Lactose	24.75	49.5
Hydroxyethyl cellulose (Natrosol 250 HX)	12.5	25
Cetostearyl alcohol	25	50
Xylitol	25	50
Hydroxypropyl cellulose (ingragranular) (klucel HF)	7.5	15
Hydroxypropyl cellulose (extragranular)	2.5	5
Sodium carboxymethyl cellulose (extragranular) (Blanose 7MFD)	2.5	5
Water		60

This process afforded one thousand 200 mg. tablets, each containing 0.5 mg. of buprenorphine.

Example 8

The method of Example 6 was repeated with the following ingredients,

Ingredient	%	Weight (g)
Phenazocine hydrobromide	5	10
Anhydrous Lactose	10	20
Hydroxyethyl cellulose (Natrosol 250 HX)	15	30
Cetostearyl alcohol	30	60
Mannitol	27.5	55
Hydroxypropyl cellulose (intragranular) (klucel HF)	7.5	15
Hydroxypropyl cellulose (extragranular)	5	10
Water		70

This process afforded one thousand 200 mg. tablets, each containing 10 mg. of phenazocine hydrobromide.

Referring to Figure 1, a kidney-shaped oral vehicle according to this invention (1) has a convex side (2) and a concave side (3). Both the upper portion (4) and the lower portion (5) of the vehicle are rounded.

In use the oral vehicle is placed in the buccal cavity of a patient, with the concave side (3) uppermost.

CLINICAL TRIALS

A comparative single dose pharmacokinetic study of three morphine sulphate preparations, namely morphine sulphate 10 mg. buccal tablets - (prepared as described in Example 1), morphine sulphate liquid 10 mg, and a sustained release morphine sulphate oral tablet 10mg (orally administered MST CONTINUS tablet) was conducted using four patients for each preparation. Morphine levels in plasma were determined using a liquid-solid extraction followed by radio immuno-assay. The results are given in Figure 2.

From this Figure it can be seen that the bioavailability of morphine sulphate is significantly prolonged using the present buccal tablets, compared with the bioavailability achieved by either a liquid morphine formulation or an orally administered sustained release morphine formulation.

A single dose pharmacokinetic study of morphine sulphate buccal tablets, 10 mg and 20 mg, was conducted using nine patients. The tablet was placed in position in the buccal cavity four hours prior to laparoscopy. Morphine levels in plasma were determined using an LSE/RIA method. Results are given in Figure 3. Again the prolonged nature of the morphine sulphate bioavailability is apparent from this Figure.

PRODUCT ADHERENCE TO MUCOSA

Placebo tablets, prepared as described in Example 1, but with morphine sulphate replaced by lactose (10.0gm) were used to determine the adherence of tablets, prepared according to this invention, to the oral mucosa.

The trial was carried out using nine volunteers. One tablet was put in place in the buccal cavity twice daily (at 12 hour intervals), using both sides of the mouth alternatively, over a seven day period.

Subjects were asked to record the duration of each tablet in the buccal cavity. Results are given in the Table.

Table

Tablet Duration (hr)

Subject	Night	Day
1	12	9.7
2	12	8.0
3	12	7.2
4	12	5.9
5	12	11.0
6	12	8.5
7	12	10.9
8	12	8.6
9	12	Subject found tablets unacceptable
Average	12	8.4

Claims

1. A sustained release, oral pharmaceutical composition in solid unit dosage form, for application to the mucosa of the oral or nasal cavity, comprising compressed granules characterised in that the granules comprise a drug, a higher aliphatic alcohol and a hydrated water soluble hydroxyalkyl cellulose and further in that the granules are coated with a mucosa adhesive cellulose.

2. A composition according to claim 1 characterised in that the granules are coated with a powdered mucosa adhesive cellulose.

3. A composition according to either claim 1 or claim 2 characterised in that the mucosa adhesive cellulose comprises a carboxyalkyl cellulose or a hydroxyalkyl cellulose, preferably sodium carboxymethyl cellulose, hydroxypropylmethyl cellulose or hydroxypropyl cellulose.

4. A composition according to claim 3 characterised in that the mucosa adhesive cellulose comprises hydroxypropyl cellulose.

5. A composition according to any one of claims 1 to 4 characterised in that the mucosa adhesive cellulose coating comprises between 2% and 15% (w/w), especially between 4% and 10% (w/w), of the total dosage form weight.

6. A composition according to any one of claims 1 to 5 characterised in that the higher aliphatic alcohol comprises cetyl alcohol or cetostearyl alcohol.

7. A composition according to any one of claims 1 to 6 characterised in that the higher aliphatic alcohol comprises between 5% and 35% (w/w), especially between 10% and 30% (w/w), of the total dosage form weight.

8. A composition according to any one of claims 1 to 7 characterised in that the water soluble hydroxyalkyl cellulose comprises hydroxymethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose or hydroxypropylmethyl cellulose, preferably hydroxyethyl cellulose.

9. A composition according to any one of claims 1 to 8 characterised in that the water soluble hydroxyalkyl cellulose comprises between 2% and 15% (w/w), of the total dosage form weight.

10. A composition according to any one of claims 1 to 9 characterised in that the drug comprises morphine, nifedipine, phenazocine, verapamil or salbutamol, preferably morphine.

11. A composition according to any one of claims 1 to 10 characterised in that the granules further comprise between 2% and 15% (w/w), especially between 4% and 10% (w/w), of a binder comprising a carboxyalkyl cellulose or a hydroxyalkyl cellulose, preferably sodium carboxymethyl cellulose, hydroxypropylmethyl cellulose or hydroxypropyl cellulose.

12. A composition according to claim 11 characterised in that the binder comprises hydroxypropyl cellulose.

13. A kidney shaped oral vehicle comprising a sustained release, oral pharmaceutical composition according to any one of claims 1 to 12.

14. A buccal tablet comprising a sustained release, oral pharmaceutical composition according to any one of claims 1 to 12.

15. A process for the preparation of a sustained release, oral pharmaceutical composition in solid unit dosage form, the composition being adapted for application to the mucosa of the oral or nasal cavity, comprising

forming granules comprising a drug, a higher aliphatic alcohol and a hydrated water soluble hydroxyalkyl cellulose

coating the granules with a mucosa adhesive cellulose, and compressing the mucosa adhesive cellulose coated granules to give a solid unit dosage form.

16. A process according to claim 15 characterised in that the granules are formed by a process comprising mixing the drug, the water soluble hydroxyalkyl cellulose and, preferably, a binder comprising a carboxyalkyl cellulose or a hydroxyalkyl cellulose to form a drug containing mixture,

hydrating the drug containing mixture to form a wet granular mass,

drying the wet granular mass to form a dry granular mass, and

mixing the dry granular mass with a higher aliphatic alcohol.

Claims for contracting state AT

1. A process for the preparation of a sustained release, oral pharmaceutical composition in solid unit dosage form, the composition being adapted for application to the mucosa of the oral or nasal cavity, comprising

forming granules comprising a drug, a higher aliphatic alcohol and a hydrated water soluble hydroxyalkyl cellulose,

coating the granules, with a mucosa adhesive cellulose, and

compressing the mucosa adhesive cellulose, coated granules to give a solid unit dosage form.

2. A process according to claim 1 characterised in that the granules are coated with a powdered mucosa adhesive cellulose.

3. A process according to either claim 1 or claim 2 characterised in that the mucosa adhesive cellulose comprises a carboxyalkyl cellulose or a hydroxyalkyl cellulose, preferably sodium carboxymethyl cellulose, hydroxypropylmethyl cellulose or hydroxypropyl cellulose.

4. A process according to claim 3 characterised in that the mucosa adhesive cellulose comprises hydroxypropyl cellulose.

5. A process according to any one of claims 1 to 4 characterised in that the mucosa adhesive cellulose coating comprises between 2% and 15% (w/w), especially between 4% and 10% (w/w), of the total dosage form weight.

6. A process according to any one of claims 1 to 5 characterised in that the higher aliphatic alcohol comprises cetyl alcohol or cetostearyl alcohol.

7. A process according to any one of claims 1 to 6 characterised in that the higher aliphatic alcohol comprises between 5% and 35% (w/w), especially between 10% and 30% (w/w), of the total dosage form weight.

8. A process according to any one of claims 1 to 7 characterised in that the water soluble hydroxyalkyl cellulose comprises hydroxymethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose or hydroxypropylmethyl cellulose, preferably hydroxyethyl cellulose.

9. A process according to any one of claims 1 to 8 characterised in that the water soluble hydroxyalkyl cellulose comprises between 2% and 15% (w/w), of the total dosage form weight.

10. A process according to any one of claims 1 to 9 characterised in that the drug comprises morphine, nifedipine, phenazocine, verapamil or salbutamol, preferably morphine.

11. A process according to any one of claims 1 to 10 characterised in that the granules further comprise between 2% and 15% (w/w), especially between 4% and 10% (w/w), of a binder comprising a carboxyalkyl cellulose or a hydroxyalkyl cellulose, preferably sodium carboxymethyl cellulose, hydroxypropylmethyl cellulose or hydroxypropyl cellulose.

12. A process according to claim 11 characterised in that the binder comprises hydroxypropyl cellulose.

13. A process according to any one of claims 1 to 12 characterised in that the granules are formed by a process comprising

mixing the drug, the water soluble hydroxyalkyl cellulose and, preferably, a binder comprising a carboxyalkyl cellulose or a hydroxyalkyl cellulose to form a drug containing mixture,

hydrating the drug containing mixture to form a wet granular mass,

drying the wet granular mass to form a dry granular mass, and

mixing the dry granular mass with a higher aliphatic alcohol.

14. A process according to any one of claims 1 to 13 characterised in that the mucosa adhesive cellulose, coated granules are compressed to give a kidney shaped oral vehicle.

15. A process according to any one of claims 1 to 13 characterised in that the mucosa adhesive cellulose, coated granules are compressed to give a buccal tablet.

Fig.1.

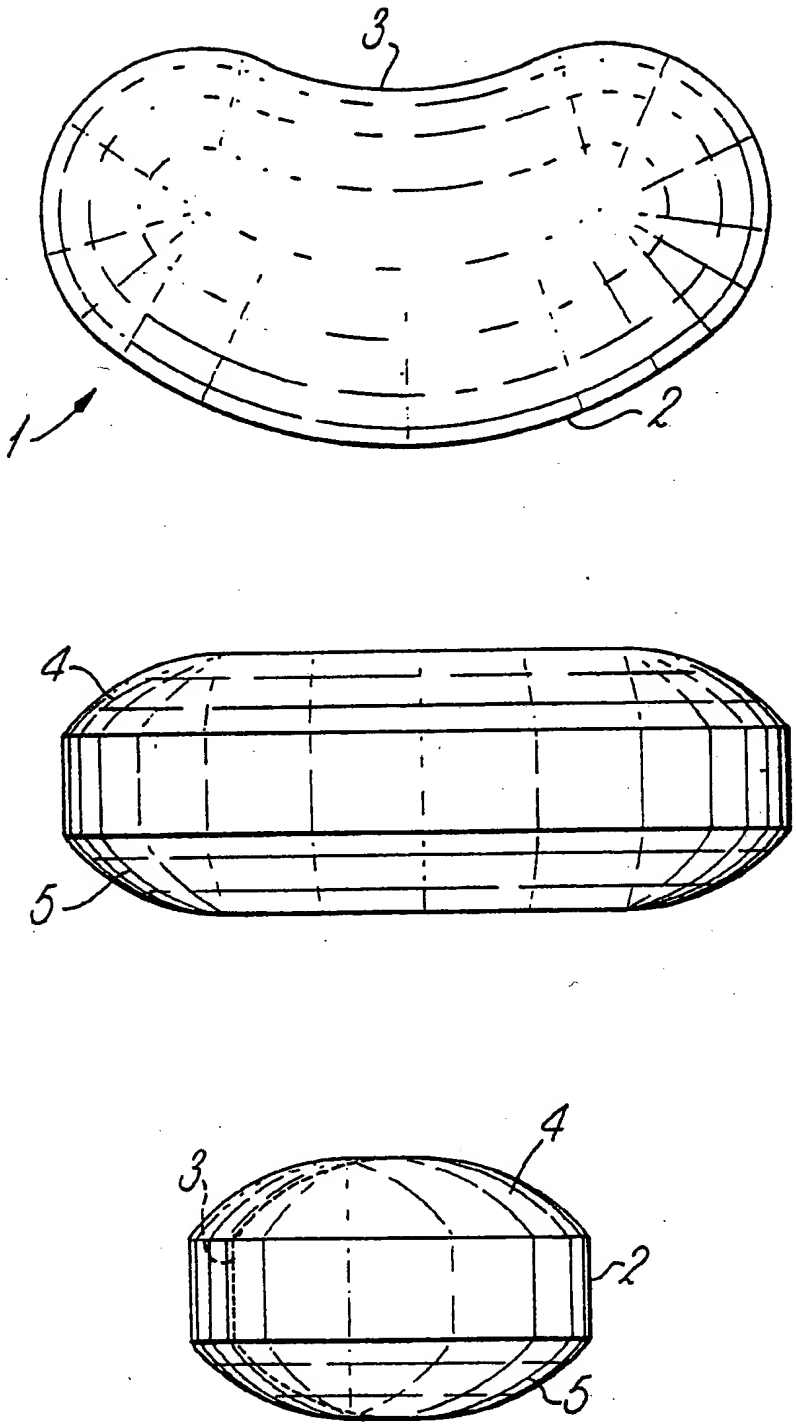
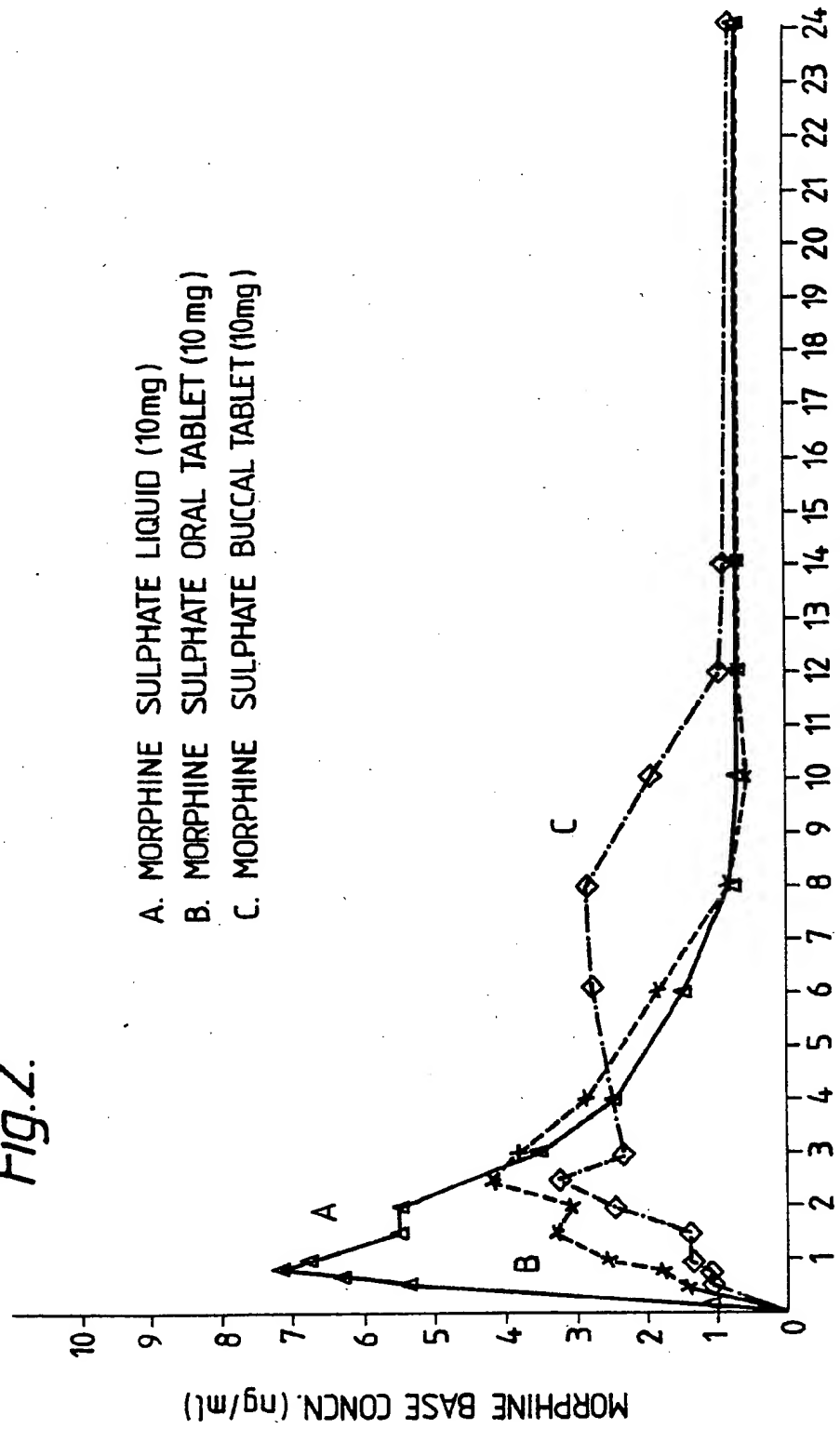


Fig.2.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C. MORPHINE SULPHATE BUCCAL TABLET (10mg)
MORPHINE BASE CONCN. (ng/ml)
TIME AFTER DOSE (hr.)
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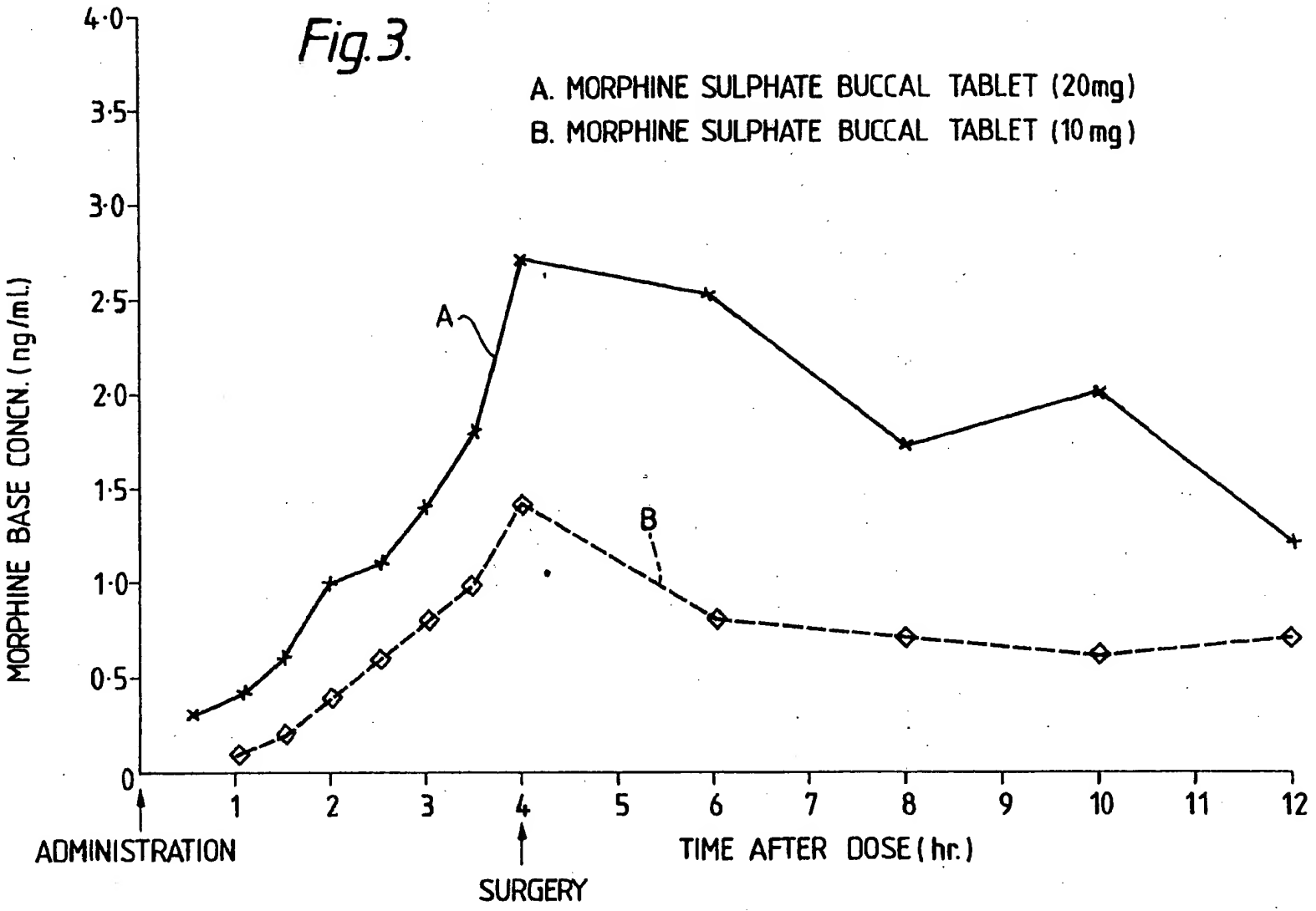
Fig.3.


A. MORPHINE SULPHATE BUCCAL TABLET (20mg)
B. MORPHINE SULPHATE BUCCAL TABLET (10 mg)
MORPHINE BASE CONCN. (ng/ml.)
4·0
3·5
3·0
2·5
2·0
1·5
1·0
0·5
0
A
B
1
2
3
4
5
6
7
8
9
10
11
12
ADMINISTRATION
SURGERY
TIME AFTER DOSE (hr.)

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